Cardiovagal modulation and oxidative stress in hypothyroidism on maintenance therapy

Modulation cardiovasculaire et stress oxydatif dans l'hypothyroïdie sous traitement d'entretien

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Abstract

Aim: To analyze the autonomic control of heart rate variability (HRV) in subjects with peripheral hypothroidism undergoing hormone replacement therapy with L-thyroxine (L-T4) for 5-10 years.

Methods: Thyroid profile, lipid profile, lipid-risk factors, parameters of oxidative stress [malondialdehyde (MDA)], inflammation [high-sensitive C-reactive protein (CRP)] and Heart rate variability (HRV) was analyzed in thirty-eight hypothyroid patients on treatment for more than five years and compared with healthy euthyroid volunteers of similar age, gender, and body composition. The link of oxidative stress with HRV parameters was assessed by Spearman-Rho correlation and regression analyses.

Results: Hypothyroid patients on L-T4 treatment, had higher TSH ($p<0.01$), lipid profile ($p<0.05$) and lipid risk factors ($p<0.05$), high-sensitive C-reactive-protein (hsCRP) (3.31 versus 4.95 mg/L; $p<0.05$) and MDA (2.66 versus 6.87 µm/L; $p <0.001$) in serum. There was gross reduction in HRV parameters [reduced standard deviation of NN interval (SDNN), root mean square of successive differences between normal heartbeats (RMSSD), total power (TP) and elevated ratio of low to high frequency power (LF/HF ratio)] in patients. Elevated MDA was correlated with vagal withdrawal (decreased SDNN, RMSSD and TP) and TSH. In multiple regression analysis TSH and TP contributed to the rise in MDA.

Conclusion: Hormone replacement therapy with L-T4 for hypothyroidism alone does not resolve persistent hyperlipidemia, oxidative stress and inflammation in primary hypothyroid patients even after five years of treatment. Association of oxidative stress with reduced cardiovagal modulation in these patients suggests persistence of cardiovascular risk despite standard treatment which warrants further investigation.

Key words: cardiovagal modulation, oxidative stress, hyperlipidemia, inflammation, total power, body composition

Résumé

Objectif : Analyser le contrôle autonome de la variabilité de la fréquence cardiaque (VRC) chez des sujets atteints d'hypothroïdie périphérique subissant un remplacement hormonal traitement à la L-thyroxine (L-T4) pendant 5 à 10 ans.

Méthodes: Profil thyroïdien, profil lipidique, facteurs de risque lipidique, paramètres de stress oxydatif [malondialdéhyde (MDA)], inflammation [haute sensibilité protéine C-réactive (CRP)] et la variabilité de la fréquence cardiaque (HRV) ont été analysées chez trente-huit patients hypothyroïdiens sous traitement pendant plus de cinq ans et par rapport à des volontaires sains euthyroïdiens d'âge, de sexe et de composition corporelle similaires. Le lien du stress oxydatif avec la HRV paramètres ont été évalués par des analyses de corrélation et de régression de Spearman-Rho.

Résultats : Les patients hypothyroïdiens sous traitement L-T4, avaient une TSH plus élevée ($p<0,01$), un profil lipidique ($p<0,05$) et des facteurs de risque lipidiques ($p<0,05$), une sensibilité élevée Protéine C réactive (hsCRP) (3,31 versus 4,95 mg/L ; $p<0,05$) et MDA (2,66 versus 6,87 µm/L ; $p <0,001$) dans le sérum. Il y a eu une réduction grossière dans les paramètres HRV [écart-type réduit de l'intervalle NN (SDNN), racine carrée moyenne des différences successives entre les battements cardiaques normaux (RMSSD), puissance totale (TP) et rapport élevé entre puissance basse et haute fréquence (rapport BF/HF)] chez les patients. Une MDA élevée était corrélée avec retrait vagal (diminution de SDNN, RMSSD et TP) et TSH. Dans l'analyse de régression multiple, la TSH et la TP ont contribué à l'augmentation de la MDA.

Conclusion : L'hormonothérapie substitutive avec L-T4 pour l'hypothyroïdie seule ne résout pas l'hyperlipidémie persistante, le stress oxydatif et l'inflammation chez les patients atteints d'hypothyroïdie primaire même après cinq ans de traitement. Association du stress oxydatif avec une réduction cardio-vagale la modulation chez ces patients suggère une persistance du risque cardiovasculaire malgré un traitement standard qui justifie une investigation plus approfondie.

Mots clés: modulation cardio-vagale, stress oxydatif, hyperlipidémie, inflammation, puissance totale, composition corporelle

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INTRODUCTION

Thyroid hormones exert a direct effect on sympathovagal tone which is reflected as sympathetic overactivity in hyperthyroid patients (1). Levothyroxine also known as L-T4 is a standard drug for replacement of thyroid hormones in primary hypothyroidism (2). Despite normalization of thyroid profile by long term treatment with L-T4, hypothyroidism is associated with chronic complications such as hyperlipidemia, secondary obesity and atherosclerotic coronary artery disease etc (3). Body composition suggesting central obesity due to higher fat content, has been linked to impaired autonomic balance (4) and hypothyroidism is associated with secondary obesity. Thyroid hormone also directly controls heart rate and exerts its effect on autonomic control via sympathetic and parasympathetic drive. Heart rate variability (HRV) analysis is a sensitive measure of autonomic dysfunctions (5) manifested as sympathovagal imbalance in humans. Though loss of sympathovagal balance have been reported earlier, some discrepancies exist among all reports (6-8) due to recruitment of newly diagnosed patients or patients treated only for six months, for comparison.

Oxidative stress has been associated with the progression of peripheral and cardiac autonomic dysfunctions in other metabolic disease such as chronic diabetes (9). It is also reported in association with the biochemical alterations in hypothyroid patients (10). Previously, we have reported oxidative stress and its association with coronary-lipid risks in treatment naïve hypothyroidism (11). Various factors such as inflammation, severity of disease, degree of hyperlipidemia and reduced antioxidants have been linked to oxidative stress in hypothyroidism. However, there are no reports of cardiometabolic profile, oxidative stress and body composition on autonomic dysfunctions in long term treated hypothyroid patients, to the best of our knowledge.

In this study, the objective was to assess HRV indices along with cardiometabolic parameters in primary hypothyroid patients on 5 to 10 years of maintenance dose of L-T4 and compare with healthy euthyroid subjects of similar age, gender and body composition.

METHODS

Study design

The study was designed as a cross-sectional (analytical) study. It was carried out as a collaboration of departments of Biochemistry, Endocrinology and Physiology, in the Institute.

Grouping of Subjects, Inclusion and Exclusion criteria

Approval of Institute Ethics Committee was obtained prior to conduct of the study. Subjects were divided into two groups: Study Group and Control Group.

Study Group: Thirty-eight primary hypothyroid patients receiving hormone replacement therapy for L-thyroxine for more than five years, having thyroid profile with TSH (normal range: 2.7-4.2 μIU/mL) below 10μIU/mL and FT3 (normal range 2-4.4 pg/mL) and FT4 (normal range 0.7-1.9 ng/dL) within normal range, age between 20 to 40 years and BMI within 18.5 to 35 Kg/m^2 were recruited for the study. Individuals with a history of smoking, alcoholism, known cases of cardiovascular disease, diabetes mellitus, renal disorder, inflammatory diseases, morbid obesity, with recent infections or severe chronic illness, hypothyroid patients on treatment for more than 10 years, patients on glucocorticoid or immuno-suppressive therapy, and pregnant or lactating ladies were excluded.

Control Group: Thirty-nine apparently healthy age, BMI and body composition matched subjects were recruited as controls. Both group participants were not on any drugs interfering with cardiovascular functions. Also, tea, coffee or other stimulating substances were restricted 6 hours before HRV analysis.

Informed Consent and Basal Recordings

The study protocol was explained to patients and healthy volunteers. All subjects were first screened clinically by the endocrinologist. Written informed consent was obtained according to the Helsinki declaration. Subjects reported to clinical biochemistry laboratory after overnight fasting. Their basal demographic and anthropometric parameters such as age, height, body weight, body mass index (BMI), Waist-Hip Ratio (WHR), systolic blood pressure (normal range 100-119 mmHg) and diastolic blood pressure (normal range 100-119 mmHg), basal heart rate (BHR) (normal range 60-100 beats per min) was recorded, and the personal history was noted using a structured proforma. Then the subjects were taken to Physiology obesity research lab for the recording of body fat composition and heart rate variability (HRV). Five ml of blood sample was collected from each. Serum was extracted and stored at –40°C for future biochemical analysis, while routine parameters such as fasting serum glucose and lipid profile was assayed on the same day.

Body composition analysis

This was recorded by Bodystat Quadscan 4000 (Bodystat, Douglas, UK) instrument that works on the principle of bioelectrical impedance using a multi-frequency-tetra polar technique. The manufacture's software displays various calculated parameters such as body fat mass %, body fat, lean body mass, body fat mass index (BFMI) and body fat-free mass index (FFMI), etc.

Biochemical parameters

Fasting serum glucose, lipid profile (triglycerides, total cholesterol, HDL- cholesterol, LDL- cholesterol & VLDL-cholesterol)–measured using commercial kits adapted to clinical chemistry autoanalyzer (Olympus 400, Beckman Coulter, Orlando, FL, USA). Thyroid profile and anti thyroperoxidase antibody titer (normal range < 16IU/mL) were estimated using commercial ultrasensitive chemiluminiscence kits (Beckman coulter).

Malondialdehyde (MDA) was estimated using thiobarbituric acid assay method colorimetrically following standard protocol.

Coronary lipid risk factors of cardiovascular disease were calculated from lipid profile values as described before (11). High sensitive C-reactive protein (hs-CRP) were analysed using solid phase sandwich assay using ELISA kits (Cal biotech, M/S bio-diagnosis, Chennai) following manufacturer's instructions.

Heart Rate Variability

For recording of short-term HRV, procedures practiced earlier[7] and recommendations of the Task Force on HRV (8) were followed. For this purpose, ECG electrodes were connected and Lead II ECG was acquired at a rate of 250 samples per second during supine rest using a BioHarness 2 data acquisition system (BIOPAC Inc, Goleta, CA, USA). The data were transferred from BioHarness to a windows-based Personal Computer (PC) with AcqKnowledge software version 4.1.0 (BIOPAC Inc, Goleta, CA, USA). Ectopics and artefacts were removed from the recorded ECG. HRV analysis was done using the HRV analysis software version 1.1 (Bio-signal Analysis group, Kuopio, Finland).

Frequency domain indices of HRV such as the total power (TP) (normal range: 600-1500 ms^2), low-frequency (LF) power expressed in the normalized unit (LFnu) (normal range: 40-60), high-frequency (HF) power expressed in the normalized unit (HFnu) (normal range: 45-65) and LF/HF ratio (normal range: 0.5-1.5), and time-domain indices of HRV such as the square root of the mean squared differences of successive normal to normal intervals (RMSSD) (normal range: 40-100), standard deviation of normal to normal interval (SDNN) (normal range: 35-90), the number of interval differences of successive NN intervals greater than 50 ms (NN50) (normal range: 30-80), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) (normal range: 10-25) were recorded.

Data Analysis

All data was expressed as mean and SD. Data was analyzed using SPSS (Chicago, IL, USA) software package version 16. Data distribution was checked by Kolmogrove Smironoff test for normality and skewness. Comparison between control and test group was done by Student's *t* test for continuous parametric data by Mann Whitney U test for nonparametric data. The strength of correlation among parameters was analysed by spearman rho correlation for non-parametric data. Independent contribution of related parameters was analysed by linear regression analysis. The level of significance was set at P <0.05.

RESULTS

The control subjects were similar in age, body mass index, waist-hip ratio and body composition parameters (Table 1 and 3). Free T3 was low (p<0.05) while TSH was higher (p<0.001) than control (Table 1). There was no difference in the serum glucose and HDL cholesterol (HDL-C), while other parameters of lipid profile and lipid risk factors were higher in chronic hypothyroid patients (Table 1).

Table 1: Comparison of anthropometric parameters, thyroid profile, and biochemical parameters between Control (euthyroid) and Study (chronic hypothyroid) groups.

	Control Group	Study Group	p
	(n= 39)	(n= 38)	
General parameters			
Age (Years)	27.30±6.79	30.18±8.47	0.104
BMI (Kg/m^2)	23.89±5.21	24.85±5.14	0.501
WHR	0.86±0.03	0.87±0.03	0.297
Thyroid profile			
FT3 (pg /mL)	3.17 ± 0.34	2.90±0.69	0.033
FT4 (ng /dL)	0.88 ± 0.10	0.76 ± 0.32	0.041
TSH (µIU/mL)	1.82 (1.26; 2.42)	3.93 (1.76; 9.22)	0.000$^{\Psi}$
Glucose and lipid profile			
Glucose (mg /dL)	80.59±9.83	85.87±14.30	0.088
TC (mg /dL)	159.20±23.07	181.65±43.84	0.015
HDL C (mg /dL)	43.00±8.08	41.52±5.90	0.406
LDL C (mg /dL)	98.89± 19.69	118.79 ±43.74	0.025
TG (mg /dL)	86.53±35.37	106.62 ±43.02	0.047
Lipid risk factors			
Non HDL-C	116.20±23.87	139.14±44.23	0.014
TG/ HDL- C	2.10±0.93	2.62±1.09	0.045
TC/ HDL-C	3.80±0.78	4.43±1.17	0.015
LDL-C/ HDL-C	2.38±0.65	2.91±1.12	0.028
AIP	0.28±0.20	0.38±0.15	0.017

The values are presented as Mean & standard deviation (SD) for parametric and as Median with interquartile range for nonparametric data. Comparison is done via Student's unpaired 't' test for parametric data and by Mann Whitney test for non-parametric data. P < 0.05 was considered significant. BMI: body mass index; WHR: Waist hip ratio; TSH: Thyroid stimulating hormone; TC: Total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: Triacyl glycerol; AIP: Atherogenic index of plasma: log (TG/ HDL- C).

The oxidative stress marker (malondialdehyde; p<0.001) and inflammatory marker (hs-CRP; p<0.05) were higher in patients (Table 2).

Table 2: Comparison of parameters of oxidative stress and inflammation between Control (euthyroid) and Study (chronic hypothyroid) groups.

	Control Group	Study Group	p
	(n= 39)	(n= 39)	
OS and inflammatory parameters			
Serum MDA (µm/L)	2.66 (2.05; .87)	6.87 (4.51; 8.20)	0.000$^{\Psi}$
HsCRP (mg/L)	3.31±2.42	4.95±3.64	0.025

The values are presented as Mean & standard deviation (SD) for parametric and as Median with interquartile range for nonparametric data. Comparison is done via Student's unpaired 't' test for parametric data and by Mann Whitney test for non-parametric data. P < 0.05 was considered significant. MDA : Malondialdehyde; hsCRP: high sensitive C reactive protein.

There was a moderate increase in basal heart rate, systolic and diastolic blood pressure, in hypothyroid patients (Table 3). Among the frequency domain parameters of autonomic function test LFnu and LF/HF ratio were higher while HFnu and total power (TP) were lower. Among the time domain indices of autonomic function test, SDNN, RMSSD ($p<0.001$), NN50 ($p<0.01$), and pNN50 ($p<0.05$) were significantly reduced in chronic hypothyroid patients (Table 3). Though there was no difference in the resting basal metabolism, the active metabolism was significantly low in these patients (Table 3).

Table 3: Heart rate, blood pressure, indices of heart-rate variability (HRV) and body composition parameters between Control (euthyroid) and Study (hypothyroid patients on prolonged treatment) groups.

	Control Group	Study Group	p
	(n= 39)	(n= 38)	
HR and BP Parameters			
BHR (beats per min)	70.01 ±9.81	74.41 ±9.25	0.041
SBP (mmHg)	118.65 ±7.03	122.58 ±7.97	0.035
DBP (mmHg)	79.48 ±3.48	82.71 ±6.64	0.017
Frequency-domain Indices of HRV			
TP (ms^2)	1207.90±719.85	775.61 ±508.30	0.019
LFnu	50.12 ±19.08	62.06 ±22.11	0.048
HFnu	50.38 ±20.37	37.52 ±16.54	0.014
LF/HF	1.24 ±0.87	2.11 ±1.45	0.019
Time-domain Indices of HRV			
SDNN (ms)	78.80 (67.30; 125.00)	35.65 (30.72; 46.65)	0.000$^{\Psi}$
RMSSD (ms)	79.10 (66.30; 124.40)	27.75 (22.70; 35.87)	0.000$^{\Psi}$
NN50 (ms)	67.73±30.20	36.54±30.62	0.002
pNN50 (ms)	13.70 (7.60; 44.50)	9.30 (6.70; 20.90)	0.011$^{\Psi}$
Body composition parameters			
Body fat (%)	32.87 ±6.58	35.07 ±5.41	0.186
BFMI	8.23 ±3.56	8.95 ±2.95	0.421
LBM (%)	67.50 ±6.14	64.89 ±5.61	0.117
FFMI	15.97 ±2.17	15.75 ±2.04	0.705
Basal metabolism	1364.30 ±151.51	1319.90 ±143.01	0.287
Active metabolism	2015 (1722; 2146)	1798 (1613; 1949)	0.030$^{\Psi}$

The values are presented as Mean & standard deviation (SD) for parametric and as Median with interquartile range for nonparametric data. Comparison is done via Student's unpaired 't' test for parametric data and by Mann Whitney test for non-parametric data. $P < 0.05$ was considered significant. BHR: Basal heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TP: Total power of HRV, LFnu: Normalized low-frequency power of HRV; HFnu: Normalized high-frequency power of HRV; SDNN: Standard deviation of normal to normal interval; RMSSD: Square root of the mean of the sum of the squares of the differences between adjacent NN intervals; BFMI: Body fat mass index; LBM: Lean body mass; FFMI: Free fat mass index.

Table 4 shows the spearman rho analysis where the rise in MDA was positively linked to TSH level and negatively to SDNN, RMSSD and TP. In subsequent regression analysis (table 5), TSH and TP independently contributed to the rise in MDA.

Table 4: Spearman correlation analysis of serum MDA with TSH and HRV parameters in Study (chronic hypothyroid) group.

Parameters	Study Group	
	r	P
TSH	0.464	0.005
TP	0.572	0.001
SDNN	−0.573	0.000
RMSSD	−0.353	0.044

$P < 0.05$ was considered significant. TSH: Thyroid stimulating hormone; TP: Total power; SDNN: Standard deviation of normal to normal interval; RMSSD: Square root of the mean of the sum of the squares of the differences between adjacent NN intervals.

Table 5: Multiple regression analysis to assess the independent association of MDA (as dependant variable) with HRV parameters (as independent variables) in Study (chronic hypothyroid) group.

Independent variable	Standardized regression	95% confidence interval		P Values
	Coefficient beta	Lower limit	Upper limit	
TSH	0.432	0.071	0.425	0.035
TP	–0.410	−0.005	0.000	0.006
SDNN	–0.122	−0.093	−0.038	0.065
RMSSD	–0.122	−0.093	−0.038	0.075

The p value <0.05 was considered significant. TSH: Thyroid stimulating hormone; TP: Total power; SDNN: Standard deviation of normal to normal interval; RMSSD: Square root of the mean of the sum of the squares of the differences between adjacent NN intervals.

DISCUSSION

In primary hypothyroid patients on maintenance therapy with L thyroxine for more than five years, there was higher degree of dyslipidemia, lipid risk factors of cardiovascular disease, oxidative stress and inflammation compared to controls (Table 1). Majority of the previous reports had follow-up studies for more than six months in such patients. However, in long term thyroxine supplemented patients these parameters have not been reported before. In a

previous study (12), the altered lipid profile was suggested to be the result of a reduced LDL receptor expression on the membrane with decreased LDL clearance.

However, Duntas et al had suggested that the lipid lowering effect is more prominent in hypothyroid patients with TSH level above 10 µU/mL (13). As our study group consists of hypothyroid patients who have continued treatment for years with TSH <10 µU/mL and FT3, FT4 within normal range, the persistence of hyperlipidemia requires further study. The lipid risk factors in our study group were also significantly higher. Thus, presence of high lipid risk factors associated with oxidative stress and hsCRP, the marker of CV risk, indicate that these hypothyroid patients in-spite of continued treatment are at high cardiometabolic risks.

From the previous reports (10,12,14), it was not clear whether the standard HRT alone can revert the oxidative stress and inflammation. In the present study, in the hypothyroid group the TSH was elevated in-spite of the normalized thyroid hormone levels in circulation. Previously TSH level was observed to have a linear relationship with OS (15) though the authors did not study its association with cardiovagal modulation. In the present study MDA was positively linked to both TSH and reduced parameters of HRV (Table 4 and 5). Therefore, even mild form of severity in the disease should not be overlooked as it could be the cause for persistence of OS in the long run despite administration of standard HRT. Fourteen out of thirty-eight patients in our study were positive for anti-thyro-peroxidase antibody (data not shown). This could be another reason for the persistence of higher OS in our findings (16). Nevertheless, we assume that it is the free radical accumulation due to reduced clearance rate in hypometabolic state of hypothyroidism and not its hyperproduction could be the reason of accumulating oxidative stress. We propose this mechanism based on significantly low activity metabolism in study group subjects (Table 3) suggesting a hypometabolic state though basal metabolism was similar.

To date, no study has been conducted on the assessment of HRV in hypothyroid patients who are continuously treated for more than five years. HRV analysis is a sensitive measure of autonomic dysfunctions (5, 17). Total power (TP) is the overall reflection of heart rate variability, LFnu is the measure of cardiac sympathetic drive, HFnu is marker of cardiac vagal drive and LF-HF ratio is the indicator of sympathovagal balance or imbalance (18). As reported by us earlier and by others, there is sympathovagal imbalance in hypothyroid patient (6,7). Lakshmi et al had reported the decrease in parasympathetic activity in hypothyroid patients, which was significantly increased on achieving euthyroid state. They had also observed that the sympathetic activity was within normal limits during hypothyroidism, which was further improved after supplementation of L-thyroxine. In our study, TP was significantly reduced, and LF-HF ratio was significantly increased in hypothyroid group indicating that these regularly treated hypothyroid patients have decreased heart rate variability and considerable sympathovagal imbalance. Celik et al had reported no change in autonomic functions in hypothyroid patients treated successfully for six months (8), while both Karthik et al and Lashmi et al had recruited freshly diagnosed hypothyroid patients (6,7). In the present study, we have analysed HRV in chronic hypothyroid patients on standard treatment for more than five years. Our findings of the present study indicate decreased cardiovagal modulation in these patients as there was significant reduction in all the time-domain indices (SDNN, RMSSD, NN50 and pNN50) of HRV that represent cardiac vagal drive. This alteration in autonomic functions with reduction in cardiovagal modulation has not been reported earlier in hypothyroid patients corrected routinely for thyroid profile, with HRT given for several years.

Hypothyroidism leads to weight gain as BMR is decreased, and development of edema in hypothyroidism occurs due to accumulation of mucopolysaccharides (19). As BMI is known to influence HRV (7, 20), in the present study, we had recruited control subjects matched for body fat composition of the study group patients, which is a merit of the present study. Karmisholt et al had observed a significant decrease in FFM with an unaltered fat mass one year after LT4 treatment induction (21), which was attributed to loss of accumulated water. Stangiersk et al stated that LT4 inhibited the lipogenesis and enhanced lipolysis due to an increased body energy demands and faster metabolism (22). We have assessed body composition based on bioelectric impedance where total body water and metabolic rate are also derived based on the electric signal generated by different cell content. We have calculated not only total fat percentage but also the free fat mass index (FFMI), which takes into account of total body weight. Nevertheless, as the patients in the present study were matched for BMI, WHR and body composition parameters, our findings suggest that the increase in oxidative stress, inflammation

(Table 2) and autonomic dysfunction (Table 3) is probably independent of the degree of adiposity.

Findings of the present study suggest that though sympathovagal imbalance improves with successful treatment in newly diagnosed hypothyroid patients (7), in the long run the imbalance becomes more prominent with a predominance of vagal inhibition and sympathetic activation. As there was negative correlation between the TSH and parameters of cardiovagal inhibition (SDNN, RMSSD and TP) in test group (Table 4), it is suggested that the autonomic dysfunction is linked to the disease severity. In these patients elevated level of TSH was in the range of subclinical hypothyroidism, which was correlated with decreased cardiovagal modulation (TP, SDNN and RMSSD) and oxidative stress (increased MDA). Further, MDA was significantly correlated with all parameters of decreased cardiovagal modulation (TP, SDNN and RMSSD), while TSH and TP contributed independently to OS in the multiple regression analysis (Table 5). These findings indicate that the persistence of OS in hypothyroid patients despite usual correction of thyroid profile, and its association to cardiovagal inhibition (decreased TP) indicates future CV risk. As lack of endogenous capacity to maintain FT4 in hypothyroid is a lifelong feature, the associated vagal inhibition in these patients make them vulnerable to high risk of cardiovascular disease despite being on L-T4 supplementation for hypothyroidism. Therefore, autonomic function tests and assessment of markers of oxidative stress and inflammation may be considered to be the part of monitoring of hypothyroid patients on prolonged treatment to assess their CV risks.

Limitations of the study

Our study population included hypothyroid patients with both normal (n=24) and elevated (n=14) TSH yet < 10μIU/mL in a proportion of 24:14. As elevated TSH < 10μIU/mL is associated with an alteration of lipid and oxidative stress parameters, their inclusion in the present study is a limitation.

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